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REVIEW ARTICLE

Adenosine A_{2A} Receptor Antagonists in Parkinson's Disease: Progress in Clinical Trials from the Newly Approved Istradefylline to Drugs in Early Development and Those Already Discontinued

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Abstract Neurotransmitters other than dopamine, such as norepinephrine, 5-hydroxytryptamine, glutamate, adenosine and acetylcholine, are involved in Parkinson's disease (PD) and contribute to its symptomatology. Thus, the progress of non-dopaminergic therapies for PD has attracted much interest in recent years. Among new classes of drugs, adenosine A_{2A} antagonists have emerged as promising candidates. The development of new highly selective adenosine A_{2A} receptor antagonists, and their encouraging anti-parkinsonian responses in animal models of PD, has provided a rationale for clinical trials to evaluate the therapeutic potential and the safety of these agents in patients with PD. To date, the clinical research regarding A_{2A} antagonists and their potential utilization in PD therapy continues to evolve between drugs just or previously discontinued (preladenant and vipadenant), new derivatives in development (tozadenant, PBF-509, ST1535, ST4206 and V81444) and the relatively old drug istradefylline, which has finally been licensed as an anti-parkinsonian drug in Japan. All these compounds have been shown to have a good safety profile and be well tolerated. Moreover, results from phase II and III trials also demonstrate that A_{2A} antagonists are effective in reducing *off-time*, without worsening troublesome dyskinesia, and in increasing *on-time* with a mild increase of non-troublesome dyskinesia, in patients at an advanced stage of PD treated with L-DOPA. In addition, early findings suggest that A_{2A} antagonists might also be efficacious as monotherapy in patients at an early stage of PD. This review summarizes pharmacological and clinical data available on istradefylline, tozadenant, PBF-509, ST1535, ST4206, V81444, preladenant and vipadenant.

Key Points

The beneficial effects of A_{2A} receptor blockade on motor deficits have been demonstrated in several experimental rodent and non-human primate models of PD. These results suggest that co-treatment with an A_{2A} antagonist plus L-DOPA reduced L-DOPA-induced *wearing-off* without worsening dyskinesia, and co-administration with a low dose of L-DOPA induced an improvement of motor symptoms with less dyskinesia

Adenosine A_{2A} antagonists are effective in reducing *off-time*, without worsening dyskinesia, in patients at an advanced stage of PD treated with L-DOPA

Adenosine A_{2A} antagonists are effective in improving motor impairments during the *on-time* in PD patients treated with L-DOPA

Istradefylline was the first adenosine A_{2A} receptor antagonist to be approved globally, for *wearing-off* phenomena in PD patients on concomitant treatment with L-DOPA-containing products, in Japan in 2013

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1 Introduction

Parkinson's disease (PD) is a common, age-related, progressive, neurodegenerative, neurological disease characterized by bradykinesia, resting tremor, rigidity, postural instability and a variety of non-motor symptoms (including sleep disturbance, depression, and cognitive decline) [1, 2]. The pathophysiological hallmark of PD is the degeneration of the dopaminergic nigrostriatal pathway, which projects to the striatum. This leads to functional modifications within the basal ganglia (BG) circuitry, which is responsible for the integration of sensorimotor information that controls voluntary movement [1]. However, neurotransmitters other than dopamine are involved in the disease and contribute to its symptomatology. These include norepinephrine, 5-hydroxytryptamine, glutamate, adenosine, and acetylcholine [3, 4].

The primary cause of dopamine neurodegeneration in PD is unknown, but evidence suggests that it might be multifactorial in terms of both aetiology and pathogenesis. A combination of environmental and genetic factors, toxins, genetic susceptibility and the aging process may be involved in PD aetiology [5]. Specifically, known contributing factors to PD pathogenesis include oxidative damage, mitochondrial dysfunction, anomalous protein aggregation, and neuroinflammation [6]. These processes, once initiated, continue to cause dopaminergic neuron damage, and have a negative impact on the efficacy of dopamine-replacement therapy.

1.1 Current Treatment of Parkinson's Disease (PD)

Current PD treatments focus on the management of symptoms with dopaminergic therapies, such as the dopamine precursor L-3,4-dihydroxyphenylalanine (L-DOPA) (in combination with a peripheral decarboxylase inhibitor), and dopamine agonists [7]. Although L-DOPA is of profound benefit in patients with PD, with time, the duration of its effect shortens (known as *wearing-off*), responses become less predictable (with rapid switching between time spent by patients in a state of mobility [*on-time*] and immobility [*off-time*]); and involuntary muscle movements (dyskinesia) or, in extreme circumstances, dystonia (a painful, involuntary spasm of muscles in various parts of the body that can be more debilitating than the underlying disease state) can develop [7].

Management of these motor fluctuations and dyskinesia currently involves combinations of regular and controlled-release L-DOPA, with the addition of a catechol-*O*-methyltransferase (COMT) inhibitor or a monoamine oxidase B (MAO-B) inhibitor, or use of a long-acting dopamine agonist or high-dose amantadine [8]. However, these medications do not completely solve the L-DOPA-induced motor complications. Furthermore, although deep brain stimulation or lesion surgery is effective in improving motor function and motor-related complications in PD, these surgical treatments are an option restricted to a defined patient population [9].

1.2 Adenosine A_{2A} Receptor Antagonists

These issues clearly highlight the urgent medical need for an alternative form of therapeutic intervention that can alleviate the symptoms of the disease, while additionally offering a reduced incidence of side effects. To date, among the non-dopaminergic therapies explored for the treatment of PD, the adenosine A_{2A} receptor antagonists seem very promising for two major reasons: their selective and restricted localization in the BG circuitry; and their interaction with dopaminergic receptors (a direct interaction with dopaminergic D_2 receptors and an indirect interaction with dopaminergic D_1 receptors) [10]. Indeed, the selective localization of A_{2A} receptors within the BG and their scarce presence in other brain areas offers a unique opportunity to modulate motor functions without producing the non-specific side effects associated with adenosine antagonism.

The adenosine A_{2A} receptors counteract functionally and are co-expressed with dopaminergic D_2 receptors on the dendritic spines of GABAergic medium spiny neurons of the indirect BG pathway projecting from the striatum to the globus pallidus [11]. Thus, A_{2A} receptor blockade leads to locomotor activation by reducing the inhibitory output of the BG indirect pathway, similar to dopamine D_2 receptor activation [10]. Moreover, very few striatonigral neurons of the 'direct' pathway, projecting from the striatum to the substantia nigra pars reticulata (SNr), express A_{2A} receptors [12]. However, activation or blockade of A_{2A} receptors in the indirect striatopallidal pathway impairs or facilitates dopaminergic D_1-mediated responses, respectively, as well [10].

Moreover, considering the neuromodulatory role of adenosine, A_{2A} receptors have been shown to interact either directly or indirectly with several receptors, such as dopamine D_3, metabotropic glutamate 4 ($mGLU_4$) and 5 ($mGLU_5$), *N*-methyl-D-aspartate, cannabinoid, 1,5-hydroxytryptamine 1A receptors and to form heteromeric complexes with some of them [13–18].

1.3 Adenosine A_{2A} Receptor Antagonists Evaluated in Clinical Trials

Several highly selective A_{2A} antagonists, both xanthine and non-xanthine derivatives, have been produced, and some of them are being tested as treatment for patients with PD in

different phase clinical trials [16, 19–22]. The research in this field continues to evolve between drugs just or previously discontinued, new derivatives in development and the relatively old drug istradefylline, which has finally been licensed as an anti-parkinsonian drug in Japan.

To date, A_{2A} antagonists have progressed to clinical trials by different pharmaceutical companies including the newly approved ***istradefylline*** (KW-6002; 8-[2(E)-(3,4-dimethoxyphenyl)vinyl]-1,3-diethyl-7-methylxanthine) from Kyowa Hakko Kirin Co. Ltd, ***PBS-509*** from Palo-Biofarma S.L., ***ST1535*** (2-butyl-9-methyl-8-(2H-1,2,3-triazol-2-yl)-9H-purin-6-ylamine) and its metabolite ***ST4206*** (4-(6-amino-9-methyl-8-(2H-1,2,3-triazol-2-yl)-9H-purin-2-yl)-butan-2-one;) from Sigma-Tau, ***tozadenant*** [SYN115; 4-hydroxy-4-methyl-piperidine-1-carboxylic-acid-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide)] from Biotie Therapies and UCB Pharma S.A., ***V81444*** from Vernalis plc; the just discontinued ***preladenant*** (SCH 420814/MK-3814; 2-(furan-2-yl)-7-[2-[4-[4-(2-methoxyethoxy)phenyl]piperazin-1-yl]ethyl]-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidin-5-amine) from Merck & Co Inc. (following its acquisition of Schering-Plough Corp.), and the previously discontinued ***vipadenant*** (BIIB014/V2006; 3-(4-Amino-3-methylbenzyl)-7-(2-furyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine) from Vernalis plc-Biogen Idec. The chemical structures of these compounds are shown in Fig. 1.

Other companies working in this field are Adenosine Therapeutics, Neurocrine Biosciences and Almirall Prodesfarma, Heptares Therapeutics and Lundbeck, although very little is known about their drugs in development at this stage [16, 23].

2 Strategy Search

The following databases were searched without date restrictions up to February 15, 2014: PubMed, Cochrane Library, ClinicalTrials.gov and Google Scholar. The search terms used included: istradefylline, KW-6002, preladenant, SCH 420814, MK-3814, tozadenant, SYN115, vipadenant, BIIB014, V2006, PBF-509, V81444, ST1535 and ST4208, adenosine A_{2A} receptor antagonist, Parkinson's disease and synonyms, clinical trials. Moreover, the references of all primary studies in all academic journals have been checked. In addition, all websites of the companies mentioned in the above subsection, in particular, the 'new press' or 'news releases' of these companies reporting data of clinical trials of A_{2A} antagonists, have been checked and reported. Finally, data reported in the proceedings of most important PD conferences, such as the International Congress of Parkinsons Disease and Movement Disorders, have been checked and reported.

3 Preclinical Evidence of Clinically Investigated A_{2A} Antagonists

The beneficial effects of A_{2A} receptor blockade on motor deficits have been demonstrated in several experimental rodent and non-human primate models of PD, including reversion of catalepsy induced by haloperidol or of hypomotility by reserpine, and modulation of turning behaviour in unilateral 6-hydroxydopamine (6-OHDA)-lesioned rodents, as well as attenuation of motor impairment in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated non-human primates [16, 20, 22, 24, 25]. Before starting clinical investigations, the above-mentioned adenosine A_{2A} antagonists were evaluated in several animal PD models to assess their anti-parkinsonian activity and pharmacokinetic and toxicological profiles [16, 19, 20, 22, 24–27]; however, as the results of these preclinical studies have not be disclosed for each A_{2A} antagonist in early clinical development, this section of the review focuses on the published findings from PD animal models of A_{2A} antagonists.

Briefly, istradefylline, preladenant, ST1535 and vipadenant produced a reversal of haloperidol-induced catalepsy in rodents, and istradefylline and ST1535 also potentiated L-DOPA effects in reducing haloperidol-elicited catalepsy [28–31]. Additionally, A_{2A} antagonists, such as istradefylline and ST1535, reduced tremulous jaw movements in rodent models of PD tremor [32, 33].

Moreover, acute administration of istradefylline, preladenant, vipadenant and ST1535 dose-dependently potentiated, in intensity and duration, contralateral turning behaviour induced by a threshold dose of L-DOPA or apomorphine in a rodent PD model of unilateral 6-OHDA lesion [20, 31, 34–36]. Hence, notably, co-administration of the A_{2A} antagonist istradefylline or preladenant with L-DOPA reversed the shortening of rotational behaviour, supporting a potential beneficial influence of A_{2A} blockade on L-DOPA-induced *wearing-off* [35, 37, Pinna unpublished observations].

Another important report showed that A_{2A} antagonists, such as ST1535 and preladenant, were effective in antagonizing specific motor deficits induced by dopaminergic neuron degeneration, such as latency of step initiation and sensorimotor integration deficits, even without L-DOPA combined administration, suggesting that these drugs would be effective as a monotherapy in the treatment of PD [38, Pinna unpublished observation].

Moreover, chronic behavioural data in unilateral 6-OHDA-lesioned rats demonstrated that preladenant and ST1535, in association with a low dose of L-DOPA, displayed anti-parkinsonian activity similar to that produced by a full dose of L-DOPA, without exacerbating sensitization of both rotational behaviour and/or abnormal

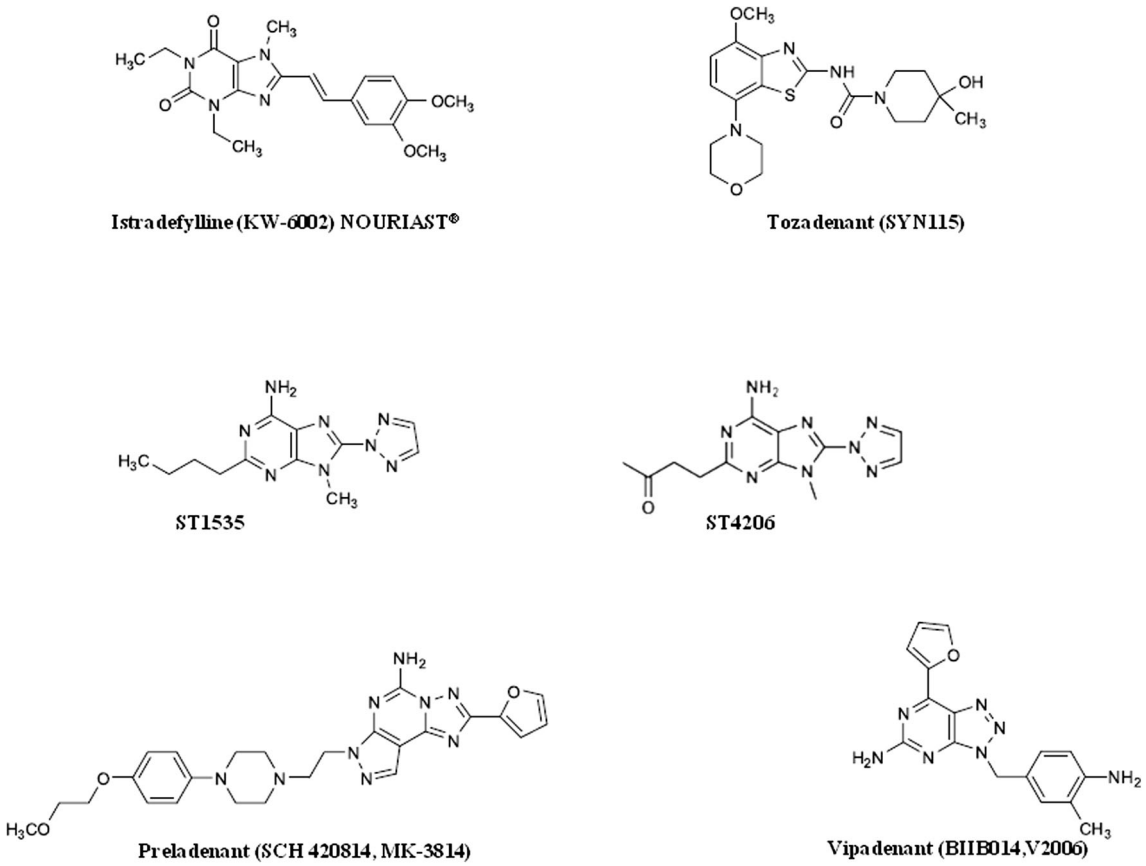

Fig. 1 Chemical structures of the adenosine A_{2A} antagonists

involuntary movements (AIMs) [31, 33]. Furthermore, repeated co-administration of istradefylline plus full dose of L-DOPA did not exacerbate the severity of the AIMs [39].

In addition, consistent with rodent studies, istradefylline, preladenant and ST1535 administered alone to parkinsonian MPTP-treated primates produced a dose-related increase in locomotor activity and an improvement in motor function, without eliciting dyskinesia [40–43]. Furthermore, when co-administered with L-DOPA, the three compounds enhanced the intensity and duration of L-DOPA-induced reversal of motor deficits in MPTP-treated primates [41–43]. Moreover, in MPTP-treated primates previously rendered dyskinetic by chronic L-DOPA, istradefylline and preladenant induced no dyskinesia per se, and when co-administered with a suboptimal dose of L-DOPA, produced a relief of motor impairment similar to that produced by an optimal dose of L-DOPA, but with less dyskinesia [41, 43, 44].

Overall, these results suggest that co-treatment with an A_{2A} antagonist plus L-DOPA reduced L-DOPA-induced *wearing-off* without worsening dyskinesia in both rodents and primates; and co-administration with a low dose of L-DOPA induced an improvement of motor symptoms with less dyskinesia. Moreover, these findings suggested that A_{2A} antagonists might be useful as monotherapy in early PD patients.

Additionally, the A_{2A} antagonists might have some neuroprotective effects, potentially slowing down disease progression. Epidemiological data that connected a high consumption of caffeine (a non-selective adenosine antagonist) with a reduced risk of developing PD, corroborate with laboratory studies showing that caffeine and more selective A_{2A} antagonists protect against dopaminergic neuron toxicity in rodent models of parkinsonian neurodegeneration [16, 22, 25, 45–48]. These data suggested a preventive action of A_{2A} antagonists on PD onset and development [16, 22, 25, 46–48]. Finally, recent results hypothesized a critical modulation of cognition by adenosine A_{2A} receptors, and A_{2A} antagonists have been proven to ameliorate cognitive dysfunction in different experimental paradigms [49, 50]. Interestingly, epidemiological studies demonstrate that regular caffeine consumption inversely correlates with cognitive decline in the elderly [51], supporting, albeit indirectly, the possibility that A_{2A} antagonists may positively impact cognitive impairment.

Table 1 Adenosine A_{2A} antagonists and their affinity for human adenosine receptors

A_{2A} antagonists	Pharmaceutical company	Ki A_{2A} (nM)	Ki A_1 (nM)	Ki A_{2B} (nM)	Ki A_3 (nM)	Phase of clinical development	References
Istradefylline	Kyowa Hakko Kirin Co Ltd	12	841	>10,000	4,470	Approved	[16, 52]
PBS-509	PaloBiofarma	ND	ND	ND	ND	Phase I	[79, 80]
ST1535	Sigma-Tau	6.6	71.8	352.3	>1,000	Phase I	[81, 83]
ST4206	Sigma-Tau	12	200	ND	ND	Phase I	[85, 86]
Tozadenant	Biotie Therapies UCB Pharma SA	4.9	1,320	ND	ND	Phase II	[16, 92]
V81444	Vernalis plc	ND	ND	ND	ND	Phase I	[95]
Preladenant	Merck & Co Inc	1.1	>1,000	>1,700	>1,000	Discontinued	[98, 113]
Vipadenant	Vernalis plc–Biogen Idec	1.3	68	63	1,005	Discontinued	[30, 124]

The table shows the affinity of different A_{2A} antagonists towards the subtypes of human adenosine receptors, and the phase of clinical development for each compound

Ki constant of inhibition, *ND* not determined

4 Effects of Adenosine A_{2A} Antagonists in Patients with PD: Results from Clinical Trials

This section focuses on data available from clinical trials of A_{2A} antagonists which are currently in progress (newly approved istradefylline; phase I for PBS-509, ST1535, ST4206 and V81444; phase II for tozadenant).

4.1 Istradefylline (NOURIAST®)

Xanthine istradefylline (KW-6002) is the first A_{2A} antagonist approved for manufacturing and marketing in Japan as a novel anti-parkinsonian medication, with the specific indication of improvement of *wearing-off* phenomena in PD patients on concomitant treatment with L-DOPA-containing products (Fig. 1) [19, 26, 52]. This encouraging result was reached after a first fail from the US Food and Drug Administration (FDA) in 2008, which did not give approval to istradefylline, expressing concern as to whether the results in clinical trials supported the clinical use of istradefylline and asking for more thorough clinical investigations [53]. However, considering the positive clinical results obtained in PD patients, the company decided to perform a further trial with istradefylline and submitted another application for manufacturing and marketing approval on March 30, 2012, in Japan [26].

Thus, istradefylline (20 mg tablets) was approved in Japan in March 2013. The usual adult dosage is 20 mg orally administered once daily, but 40 mg once daily can be used if symptoms are not well controlled. Istradefylline should always be administered concomitantly with L-DOPA [52].

Istradefylline displayed high affinity for human A_{2A} receptors, with constant of inhibition (Ki) values of 12 nM (Table 1) and higher selectivity (800-fold) for adenosine A_{2A} than for A_1 receptors in humans [19, 26].

Istradefylline is orally active and shows good pharmacokinetic properties [26]. The pharmacokinetic properties of istradefylline have been extensively quantified by a two-compartment model analysis, which included the estimation of covariate effects on istradefylline pharmacokinetic parameters, in 230 healthy and 1,219 parkinsonian subjects [54]. This population pharmacokinetic study demonstrated that the observed concentration data, obtained after administration of istradefylline at doses from 10 to 200 mg, were deemed appropriate for further evaluation of the istradefylline exposure–response relationship in patients with PD [54].

Moreover, a phase I positron emission tomography (PET) trial, using the radiotracer [^{11}C]KW-6002 in 15 healthy volunteers, has been undertaken to evaluate A_{2A} receptor occupancy in areas of the brain following oral ascending doses (0.5–40 mg/day) of istradefylline for 14 days [55]. PET results showed that A_{2A} receptor occupancy by istradefylline increased in a dose-dependent fashion, reaching more than 90 % with the dose of 5 mg/day, which is compatible with further development as a once-daily treatment [55].

4.1.1 *Clinical Trials of Istradefylline as Adjunctive Therapy*

In a phase IIa clinical trial of 6 weeks' duration, the effects of istradefylline, given in combination with intravenous L-DOPA, have been evaluated in 15 patients with moderate-to-severe PD experiencing overt motor complications [56]. Motor function was evaluated using the motor Unified PD Rating Scale (UPDRS motor). The results of this trial demonstrated that istradefylline at both doses (40 or 80 mg/day), administered in combination with a standard dose of L-DOPA, did not modify motor responses and

dyskinesia compared with those produced by L-DOPA alone [56]. However, istradefylline prolonged the half-life of the standard L-DOPA dose by an average of 47 minutes (76 %; $p < 0.05$), suggesting that it reduced the *off-time* in PD patients with motor fluctuations [56].

Conversely, the co-administration of istradefylline (80 mg/day) with a low dose of L-DOPA (which alone does not have any anti-parkinsonian effect) significantly improved motor impairment (36 %; $p < 0.02$) similar to that produced by a standard L-DOPA dose, eliciting a lower degree (45 %; $p < 0.05$) of dyskinesia (specifically choreiform dyskinesia). Indeed, the latter association led to a beneficial effect on all cardinal symptoms in PD patients, particularly on resting tremor (72 %; $p < 0.02$). The lower dose of istradefylline was also found to potentiate a low dose of L-DOPA, but with less efficacy [56].

A concomitant long-term (12 weeks) phase IIa (US-001) trial with istradefylline, at doses up to 20 (5/10/20) or 40 (10/20/40) mg/day, has been performed in ($n = 26$ and 28, respectively) advanced PD subjects treated with a standard oral dose of L-DOPA, experiencing motor fluctuations and dyskinesia [57]. Findings described in the patients' home diaries showed that both doses of istradefylline as adjunctive therapy reduced the *off-time* by about 1.2–1.7 hours compared with placebo ($p = 0.004$) [57]. Moreover, while the severity of dyskinesia remained unchanged, the *on-time* with dyskinesia was increased in the istradefylline groups compared with the placebo groups ($p = 0.002$) [57]. However, no differences were observed in the UPDRS motor scores or in the Clinical Global Impression of Change scale [57].

In order to confirm and extend the evaluation of efficacy of istradefylline in reducing *off-time*, two large phase II clinical trials (NCT00456586 and NCT00456794) were conducted in 196 and 395 advanced PD patients with motor fluctuations (specifically *wearing-off*, with or without dyskinesia), under treatment with L-DOPA, either alone or in stable combination with other PD medications (Table 2) [58–61]. In these studies, three doses of istradefylline (40 mg/day in one study and 20 and 60 mg/day in the other) were used and, similar to data obtained in phase IIa, treatment of istradefylline at all doses showed a significant decrease in *off-time* in PD patients [58–61]. Specifically, the percentage of *off-time* was significantly reduced with istradefylline 40 mg/day ($p = 0.007$), as well as with 20 or 60 mg/day ($p = 0.026$ and $p = 0.024$, respectively) [60, 61]. Moreover, in both trials, the reduction in *off-time* was apparent by 2 weeks and continued throughout the treatment [60, 61].

Interestingly, both latter clinical studies included an important measure to differentiate between 'troublesome' and 'non-troublesome' dyskinesia during *on-time* [60, 61]. In both studies, istradefylline significantly increased *on-time* with non-troublesome dyskinesia, whereas *on-time* with troublesome dyskinesia remained unchanged [60, 61].

Similar results were obtained in a wide phase III clinical trial (NCT00199407) conducted in 231 PD patients with motor fluctuations, where istradefylline 20 mg/day, as adjunctive treatment, significantly decreased *off-time* by about 0.7 hour ($p = 0.03$ compared with placebo) (Table 2) [62, 63].

Another long-term phase III clinical study (NCT00955045), lasting 52 weeks in 496 advanced PD patients who had previously completed other investigations (US-001, NCT00456586 and NCT00456794), showed that the efficacy of the drug in reducing *off-time* in doses of between 20 and 60 mg/day was maintained in patients who were already taking the drug at the start of the study, suggesting evidence of a consistent and sustained drug effect (Table 2) [64, 65].

Similar efficacy of istradefylline was shown by two Japanese phase II (NCT00455507) and III (NCT00955526) trials, with 363 and 373 advanced PD patients, respectively, in which istradefylline at 20 and 40 mg/day not only significantly reduced the *off-time*, but also improved the UPDRS motor scores compared with placebo (Table 2) [66–69]. In particular, in the phase II (NCT00455507) study, the *off-time* reduction was about 0.65 hour with istradefylline 20 mg/day ($p = 0.013$) and about 0.92 hour with 40 mg/day ($p < 0.001$) compared with placebo; moreover, the reduction on UPDRS motor scores was of 5.7 in both istradefylline groups and 3.7 in the placebo group ($p = 0.006$ for 20 and 40 mg/day as compared with placebo) [68].

In the phase III trial (NCT00955526), the *off-time* reduction was similar at both doses of istradefylline [about 0.99 hour with 20 mg/day ($p = 0.003$) and about 0.96 hour with 40 mg/day ($p < 0.003$)]; whereas, the reduction on UPDRS motor scores was significant only with istradefylline 40 mg/day ($p = 0.001$) [69].

Interestingly, a meta-analysis of five randomized controlled trials, using istradefylline at 20 and 40 mg/day, demonstrated that both doses of istradefylline were effective in reducing the daily *off-time* as well as in improving the motor UPDRS scores (symptoms) during the *on-time* in PD patients [70]. However, an increase occurs in *on-time* with dyskinesia, but most of this increase is non-troublesome dyskinesia [70].

Conversely, the phase III clinical trial (NCT00199420) that evaluated 10, 20 and 40 mg/day istradefylline in 605 patients with motor fluctuations induced by L-DOPA, did not display a significant reduction in *off-time* compared with placebo with any istradefylline doses, although a dose response was observed between the istradefylline-treated groups (10 mg: −1.0 h; 20 mg: −1.1 h; 40 mg: −1.5 h; placebo: −1.3 h) [71, 72]. However, a modest but

Table 2 Summary of clinical trials of adenosine A_{2A} receptor antagonists

Status of A_{2A} antagonist study	ClinicalTrials.gov [study phase]	Title of clinical trial	Treatment and duration	Clinical evaluations	References
Istradefylline (KW-6002) NOURIAST®					
Completed	[Proof-of-principle]	Double-bind, placebo-controlled trial of adenosine A_{2A} receptor antagonist istradefylline in advanced PD Administered alone or in combination with a standard or a low dose of L-DOPA	40, 80 mg/day 6 weeks	Changes on UPDRS motor scale, percentage of *off-time*, and severity of dyskinesia AEs frequency, clinical laboratory values and vital signs	[56]
Completed	(6002-US-001) [Phase II]	Double-blind, randomized placebo-controlled trial of safety and efficacy of istradefylline as adjunctive therapy in advanced PD	5/10/20 or 10/20/40 mg/day 12 weeks	Changes on UPDRS motor scale, percentage of *off-time*, severity of dyskinesia, and CGI-I AEs frequency, clinical laboratory values and vital signs	[57]
Completed	NCT00456586 (6002-US-005) [Phase II]	12-week, double-blind, placebo-controlled, randomized study of the efficacy of 40 mg/day istradefylline in PD patients on L-DOPA/carbidopa	40 mg/day 12 weeks	Percentage of *off-time*, changes on UPDRS scale, changes on ADL Safety	[58, 60]
Completed	NCT00456794 (6002-US-006) [Phase II]	12-week, double-blind, placebo-controlled study of 20 and 60 mg/day istradefylline in PD patients on L-DOPA/carbodopa	20, 60 mg/day 12 weeks	Reduction of *off-time*, changes on UPDRS scale, severity of dyskinesia during *on-time* and changes on CGI-I Safety	[59, 61]
Completed	NCT00199407 (6002-US-013) [Phase III]	A 12-week, double-blind, placebo-controlled, randomized, parallel group, multicenter, fixed dose study to evaluate the efficacy and safety of istradefylline in patients with motor response complications on L-DOPA/carbidopa therapy	20 mg/day 12 weeks	Percentage of *off-time,* changes on UPDRS scale, severity of dyskinesia during *on-time*, changes on CGI-I, PGI-I, and ADL Safety	[62, 63]
Completed	NCT00955045 (6002-US-007) [Phase II/phase III]	A long-term, multicenter, open-label, safety study with a flexible dose range of istradefylline as treatment for PD in patients with motor response complications on L-DOPA/carbidopa therapy	20, 40, 60 mg/day 52 weeks	Reduction of *off-time, c*hanges on UPDRS scale, severity of dyskinesia during *on-time* Safety and tolerability	[64, 65]
Completed	NCT00455507 (6002-0608) [Phase II]	Placebo-controlled, double-blind, parallel group, fixed dose study of istradefylline for the treatment of PD in patients taking L-DOPA	20 or 40 mg/day 12 weeks	Percentage of *off-time,* changes on UPDRS and CGI-I scale, severity of dyskinesia during *on-time* Safety	[66, 68]
Completed	NCT00955526 (6002-009) [Phase III]	Placebo-controlled, double-blind, parallel group, fixed dose study of istradefylline for the treatment of PD in patients taking L-DOPA	20 or 40 mg/day 12 weeks	Percentage of *off-time,* changes on UPDRS scale, severity of dyskinesia during *on-time*, changes on CGI-I Safety	[67, 69]
Completed	NCT00199420 (6002-US-018) [Phase III]	Double blind, placebo-controlled, randomized, parallel group, multicenter, fixed dose study to evaluate the efficacy and safety of oral dose of istradefylline as treatment for PD in patients with motor response complications on L-DOPA/carbidopa therapy	10, 20, 40 mg/day 12 weeks	Percentage of *off-time,* changes on UPDRS scale and CGI-I and PGI-I, severity of dyskinesia during *on-time* Safety	[71, 72]

Table 2 continued

Status of A_{2A} antagonist study	ClinicalTrials.gov [study phase]	Title of clinical trial	Treatment and duration	Clinical evaluations	References
Completed	NCT00199394 (6002-EU-007) [Phase III]	Double-blind, placebo-controlled, randomised, parallel-group, international study to evaluate the efficacy and safety of istradefylline and that of entacapone versus placebo as treatment for PD in patients with motor response complications on L-DOPA therapy	40 mg/day 16 weeks	Percentage of *off-time,* changes on UPDRS scale, severity of dyskinesia during *on-time*, changes on CGI-I and PGI-I AEs frequency, clinical laboratory values, ECG and vital signs	[73, 74]
Completed	NCT00199433 (6002-US-051) [Phase II]	Double-blind, placebo-controlled, randomized, parallel-group, multicenter study to evaluate the efficacy and safety of 40 mg/day istradefylline as monotherapy in subjects with PD	40 mg/day 12 weeks	Change from baseline in the UPDRS motor and CGI-I AEs frequency, clinical laboratory values and vital signs	[76, 77]
Completed	NCT00250393 (6002-0407) [Phase II]	Placebo-controlled, crossover, double-blind study of istradefylline in the treatment of PD [monotherapy]	40 mg/day 12 weeks	Changes on UPDRS scale, changes on CGI-I and PGI-I Safety	[129]
Completed	NCT00199355 (6002-0406) [Phase II]	Placebo-controlled, double-blind, exploratory study of istradefylline in the treatment of PD [adjunctive therapy to L-DOPA]	20 or 40 mg/day 12 weeks	Percentage of *off-time,* changes on UPDRS and CGI-I scale, severity of dyskinesia during *on-time* Safety	[130]
Completed	NCT00957203 (6002-010) [Phase III]	Long-term safety study of istradefylline in the treatment of PD	20 or 40 mg/day	Percentage of *off-time,* changes on UPDRS and CGI-I scale, severity of dyskinesia during *on-time* Safety	[131]
Terminated	NCT00199381 (6002-US-025) [Phase III]	Open-label, long-term safety extension of istradefylline in North American PD patients who have completed study 6002-INT-001	20 or 40 mg/day	AEs frequency, long-term tolerability and safety	[132]
Completed	NCT00203957 (13711A) [Phase III]	A long-term, multicenter, open-label safety study with istradefylline as treatment for PD in patients with motor response complications on L-DOPA therapy	20 or 40 mg/day 52 weeks	AEs frequency, long-term tolerability and safety	[133]
Completed	NCT00199368 (6002-INT-001) [Phase III]	Opel-label extension of istradefylline in PD patients who have completed studies 6002-EU-007, 6002-US-013 or 6002-US-018	20 or 40 mg/day 52 weeks	AEs frequency, long-term tolerability and safety	[134]
Recruiting participant	NCT01968031 [Phase III]	A 12-week randomized study to evaluate oral istradefylline in subjects with moderate to severe PD (KW-6002)	20 or 40 mg/day 12 weeks	Percentage of *off-time,* changes on UPDRS scale, severity of dyskinesia during *on-time,* changes on CGI-I and PGI-I, cognitive assessment, depression, sleep time in 1 day	[75]
PBF-509					
Completed	NCT01691924 (IIBSP-PBF-2012-38) [Phase I]	Randomized, double blind, placebo controlled "First In-human" study to assess the safety and tolerability of single ascending oral doses of PBF-509 in male healthy volunteers	10, 20, 40, 80, 160, 320, 480, 620 mg	AEs frequency, tolerability and safety and pharmacokinetic analysis	[80]

Table 2 continued

Status of A_{2A} antagonist study	ClinicalTrials.gov [study phase]	Title of clinical trial	Treatment and duration	Clinical evaluations	References
Tozadenant (SYN115)					
Completed	NCT00605553 (SYN115-CL01)	Randomized, double-blind, placebo controlled, study to explore the effects of 7 days of dosing with SYN115 on clinical and fMRI response to intravenous L-DOPA in patients with mild to moderate PD	20 or 60 mg/BID 7 days	Changes on UPDRS and tapping speed; fMRI evaluation AEs frequency, tolerability and safety and pharmacokinetic analysis	[88–90]
Completed	NCT01283594 (SYN115-CL02) [Phase II/phase III]	Double-blind, randomized, placebo-controlled study of the safety and efficacy of SYN115 of as adjunctive therapy in L-DOPA-treated PD subjects with end of dose wearing off	60, 120, 180, 240 mg/BID 12 weeks	Percentage of *off-time,* changes on UPDRS and CGI-I scale, severity of dyskinesia during *on-time* Safety and tolerability	[91, 92]
V81444					
Completed	NCT01634568 [Phase I]	A double-blind, randomised, placebo-controlled study of the safety, tolerability and pharmacokinetics of single and multiple ascending oral doses of V81444 in healthy male volunteers	Single or multiple ascending doses	AEs frequency, clinical laboratory values, ECG, vital signs and physical examination	[94, 95]
Preladenant (SCH 420814 MK-3814)					
Completed	NCT00406029 (P04501) [Phase II]	Double-blind, dose-finding, placebo-controlled study to assess the efficacy and safety of a range of SCH 420814 doses in subjects with moderate to severe PD experiencing motor fluctuations and dyskinesias	1, 2, 5, 10 mg /BID 12 weeks	Percentage of *off-time,* changes on UPDRS scale, severity of dyskinesia during *on-time* Safety and tolerability	[102, 103]
Completed	NCT01294800 (P06402) [Phase II]	A dose finding study of preladenant (SCH 420814) for the treatment of PD in Japanese patients (P06402 AM2)	2, 5 or 10 mg/BID 12 weeks	Percentage of *off-time,* severity of dyskinesia during *on-time* Safety and tolerability	[104]
Completed	NCT00537017 (P05175) [Phase II]	Follow up safety study of SCH 420814 in subjects with PD (P05175AM1)	5 mg/BID 36 weeks	Proportion of subjects reporting AEs Clinical laboratory values, ECG, vital signs and physical examination	[106, 107]
Completed	NCT00845000 (P05550) [Phase I]	Acute effects of preladenant (SCH 420814) on dyskinesia and parkinsonism in L-DOPA treated participants (P05550 AM3)	10 or 100 mg	Effect on L-DOPA-induced dyskinesia Effect on tapping score	[105]
Completed	(P044941) [Phase I]	A randomized, double-blind, positive- and placebo-controlled, four-period crossover study performed under steady-state exposure of clinical and supratherapeutic doses of preladenant (10 mg BID and 100 mg BID, respectively, for 5 days), moxifloxacin, or placebo in healthy adult volunteers	10 or 100 mg BID 5 days	Evaluation of clinical and supratherapeutic doses of preladenant on cardiac repolarization AEs frequency, clinical laboratory values, ECG, vital signs and physical examination	[112]
Completed	NCT01227265 (P07037) [Phase III]	Placebo controlled study of preladenant in participants with moderate to severe PD (P07037 AM3)	2 or 5 mg/BID 12 weeks	Percentage of *off-time,* severity of dyskinesia during *on-time* Safety and tolerability	[108]

Table 2 continued

Status of A_{2A} antagonist study	ClinicalTrials.gov [study phase]	Title of clinical trial	Treatment and duration	Clinical evaluations	References
Completed	NCT01155466 (P04938) [Phase III]	Placebo- and active controlled study of preladenant in subjects with moderate to severe PD (Study P04938 AM5)	2, 5 or 10 mg/ BID 12 weeks	Percentage of *off-time,* severity of dyskinesia during *on-time* Safety and tolerability	[109]
Terminated	NCT01215227 (P06153) [Phase III]	Active-controlled extension study to P04938 and P07037 (P06153 AM3)	2, 5 or 10 mg/ BID 40 weeks	Incidence of changes in systolic and diastolic blood pressure, AEs frequency, clinical laboratory values	[110]
Terminated	NCT01155479 (P05664) [Phase III]	Placebo- and active-controlled study of preladenant in early PD (P05664 AM5)	2, 5 or 10 mg/ BID 52 weeks	Change from baseline in the sum of UPDRS motor scores and changes of ADL Safety and tolerability	[111]
Vipadenant (BIIB014/V2006)					
Completed	NCT01017666 [Phase I]	BIIB014: effects on the pharmacokinetics of rosiglitazone, warfarin, and midazolam	100 mg/ 8 or 14 days	Pharmacokinetic profile of rosiglitazone, midazolam during exposure to BIIB014 or placebo and AEs	[115]
Completed	NCT00531193 (204HV101) [Phase I]	Using PET scans to study brain receptor occupancy of BIIB014 in healthy male volunteers	2.5–100 mg/ day 8–12 days	PET scanning with [11C]SCH442416 of the putamen, caudate, nucleus accumbens, thalamus and cerebellum	[116, 118]
Completed	NCT00438607 [Phase II]	Dose-finding safety study of BIIB014 in combination with L-DOPA in moderate to late stage PD	Single or multiple ascending doses/day 8 weeks	AEs frequency, clinical laboratory values, ECG, vital signs and physical examination	[119]
Completed	NCT00442780 [Phase II]	Dose-finding safety study in early-stage Parkinson's disease (MOBILE)	multiple ascending doses/day	AEs frequency, clinical laboratory values, ECG, vital signs and physical examination	[122]
Completed	NCT01035515 (204HV102) [Phase I]	BIIB014 cardiovascular monitoring study	50 or 100 mg	Supine blood pressure	[123]

ADL activities of daily living, *AEs* adverse effects, *BID* twice daily, *CGI* clinical global impression, *CGI-I* change scale-improvement, *ECG* electrocardiographic parameters, *fMRI* functional magnetic resonance imaging, *L-DOPA* L-3,4-dihydroxyphenylalanine, *PD* Parkinson's disease, *PET* positron emission tomography, *PGI* patient global impression, *PGI-I* patient global impression improvement scale, *UPDRS* Unified PD Rating Scale

significant improvement of UPDRS motor scores was observed with istradefylline 40 mg/day compared with placebo ($p < 0.05$) [72].

Similarly, in a longer-term (16-week) phase III trial (NCT00199394), istradefylline 40 mg/day did not significantly reduce the *off-time* compared with placebo, but showed a trend towards improvement in motor function measured by UPDRS motor scores [73, 74]. The reason for these negative results is not known, but could be due to the problem of large and maintained placebo effects in PD patients and the modest duration of the decrease in *off-time* seen during clinical development [72]. Further discussion of these negative data can be found in Sect. 6.

Lastly, in November 2013 the company initiated a global 12-week phase III (NCT01968031) trial of 20 and 40 mg/day, as adjunctive therapy, in 609 subjects with moderate-to-severe PD [75].

A few clinical trials with istradefylline demonstrated a dose response in reducing the *off-time* [56, 57, 68, 72] and, in particular, in improving the UPDRS motor scores in advanced PD patients [56, 68, 69, 72]. On the other hand, several trials showed a full efficacy of istradefylline 20 mg/day in reducing *off-time* [57, 61, 63, 69]. This finding is supported by the PET study [55] and suggested that 20 mg/day of istradefylline should be the first-choice dosage to reduce *off-time* in PD patients [52]. Moreover, 40 mg/day

or more of istradefylline might be necessary to improve the UPDRS motor scores.

4.1.2 Clinical Trials of Istradefylline as Monotherapy

In the phase IIa clinical trial of 6 weeks' duration, mentioned above, the effects of istradefylline were also evaluated as monotherapy in the 15 patients with moderate-to-severe PD with motor complications [56]. The results of this trial demonstrated that istradefylline at both doses (40 or 80 mg/day), administered alone, did not modify motor responses and dyskinesia compared with those produced by L-DOPA alone [56].

However, given the encouraging results of several preclinical studies, istradefylline 40 mg/day was compared with placebo as monotherapy in a second phase II trial (NCT00199433) involving 176 early PD patients for 12 weeks [76, 77]. Although istradefylline provided numerical improvement in UPDRS motor scores compared with placebo, the difference across groups was not statistically significant ($p = 0.228$) [77]. However, istradefylline also provided numerically greater improvement in UPDRS motor scores at each time point, and, compared with placebo, significantly greater improvement at week 2 ($p = 0.047$) [77].

The inability of istradefylline monotherapy to reverse parkinsonian disabilities in humans is in conflict with findings observed in animal models of PD, in which istradefylline or SCH58261 counteracted motor deficits when administered without L-DOPA [28, 38, 40, 41, 44]. This discrepancy may be explained by the use of lower doses of istradefylline in these clinical monotherapy trials. Indeed, specifically, the latter study was conducted at the recommended dosage (40 mg/day) for istradefylline as adjunctive therapy to L-DOPA [77]. Thus, it is possible that higher doses (more than 80 mg/day) of istradefylline, administered alone, together with the randomization of more subjects and the inclusion of subjects with worse motor disease, may elicit beneficial effects on parkinsonian symptoms. Hence, more exhaustive studies of istradefylline as monotherapy over longer periods and in larger populations may be considered. Further discussion of these negative data can be found in Sect. 6.

4.1.3 Safety and Tolerability of Istradefylline

Clinical trials performed to date have provided evidence of a suitable tolerability and safety profile for istradefylline. The most common adverse effects (AEs) were nausea (generally mild and usually lasting no more than 10 days), aggravation of dyskinesia, dizziness and insomnia [19, 56, 57, 60, 61, 63, 68, 69, 72, 77]. Other AEs rarely reported by patients were increased stiffness, vomiting, headache and hallucinations [19, 56, 57, 60, 61, 63, 68, 69, 72, 77]. Moreover, discontinuation due to AEs was infrequent and there was no difference between the placebo and istradefylline groups. No marked clinical differences were observed in systolic or diastolic blood pressure, heart rate, respiratory rate, body weight, urine and blood chemistry tests between the istradefylline and placebo groups [19, 56, 57, 60, 61, 63, 68, 69, 72, 77].

Interestingly, in the trial NCT00199420, somnolence, a common AE seen in dopaminergic PD drugs, was seen at a higher incidence in subjects treated with placebo and a low dose (10 mg) of istradefylline compared with the higher doses (20 and 40 mg) of istradefylline [72]. This effect is consistent with the role played by adenosine and A_{2A} antagonists on sleep [78]. Unfortunately, in this or in other trials, no quantification of diurnal somnolence was used to demonstrate a significant benefit of istradefylline in abating this well known side effect of dopamine agonists and L-DOPA [72]. Thus, further clinical investigations, focused on positive effect of A_{2A} antagonists on diurnal somnolence, would need to clarify this issue.

4.2 PBF-509

PBF-509 is a novel, non-xanthine potent and selective competitive antagonist of the human adenosine A_{2A} receptors [79]. Preclinical studies have been done to assess the pharmacological, pharmacokinetic, safety and toxicological profile of PBF-509 and the results of these studies demonstrated that this compound has excellent response in relevant animal models of PD at safe doses [79]. On the basis of these promising preclinical results, a double-blind, placebo-controlled, phase I clinical trial (NCT01691924) has been performed to assess the safety, tolerability and pharmacokinetic profile of single ascending oral doses of PBF-509 in 32 healthy male volunteers, at the research centre for new drugs at the Hospital de Sant Pau in Barcelona [79, 80]. The results of this phase I trial have not been disclosed yet.

4.3 ST1535 and ST4206

The development of ST1535 by Sigma-Tau started with a study aimed at generating new non-xanthine A_{2A} antagonists on the basis of the available structure–activity knowledge for A_{2A} receptor ligands [81]. ST1535 is a 9H-purine derivative with an alkyl chain useful in modulating selectivity versus A_{2A} subtype receptor, and a 1,2,3-triazole ring useful for improving the solubility profile and for providing one more H-bond acceptor relative to furan (Fig. 1) [81].

ST1535 displayed a preferential affinity to human A_{2A} adenosine receptors (Ki = 6.6 nM) compared with human

A_1 adenosine receptors, in addition to showing a 12-fold selectivity for A_{2A} receptors versus A_1 receptors, and no appreciable affinity for more than 30 different other receptors (Table 1) [81].

As described in Sect. 3, ST1535 showed good anti-parkinsonian activity in different experimental models of PD in rodents and primates; for review see [20]. Moreover, ST1535 (20 mg/kg) also reduced the passive avoidance induced by the A_1 agonist N6-cyclopentyladenosine, suggesting that ST1535 might also be effective on cognitive aspects of PD [82].

The findings from these preclinical studies have led to a phase I clinical trial being performed to establish the tolerability and safety and to collect human pharmacokinetic data on single oral ascending doses (50, 100, 200, 300 and 450 mg) of ST1535. All single doses of ST1535 were generally well tolerated. Indeed, there were no haematological, biochemical or urinary laboratory abnormalities of clinical concern [20, 83]. On the basis of the results of this phase I clinical study, it was planned to test the safety and pharmacokinetic profiles of ST1535 at multiple doses (50, 100, 150 and 200 mg/day, over 2 weeks). This study is ongoing [20, 83].

The company has also started to investigate the anti-parkinsonian activity of two metabolites of ST1535 (i.e., ST3932 and ST4206), which have shown good efficacy in a rodent model of PD (Fig. 1) [84, 85]. In particular, ST4206 has been identified as a new A_{2A} antagonist suitable for development as an anti-parkinsonian drug, being able to improve parkinsonian signs without causing or worsening dyskinesia in animal models, either as monotherapy or as an adjunct to L-DOPA [85, 86].

4.4 Tozadenant

The benzothiazole derivative tozadenant (SYN115) is a selective and potent A_{2A} antagonist that is not structurally related to xanthine or adenine [87].

After promising results achieved in experimental animal models of PD, a phase II trial (NCT00605553) with tozadenant in 30 patients with mild-to-moderate PD has been performed (Table 2) [88]. In this phase II trial of 1 week duration, administration of oral tozadenant (20 or 60 mg, twice daily [BID]), singularly or in combination with a low-dose infusion of L-DOPA, was evaluated using several techniques, including clinical ratings, such as the UPDRS motor scores, tapping speed, and the functional magnetic resonance imaging (fMRI, as a tool to rapidly evaluate the pharmacodynamic effects of the new drug in the brain) [88–90]. Results of this study showed that tozadenant at 60 mg BID significantly improved tapping speed compared with placebo, both with and without a sub-therapeutic infusion of L-DOPA [89]. Total UPDRS motor score was 20 % lower with tozadenant compared with placebo when administered with L-DOPA [89]. Considering UPDRS items individually, 10 of 13 items were better on tozadenant than on placebo; in particular, improvement in two UPDRS measures of bradykinesia (finger taps and rapidly alternating movements of the hands) obtained statistical significance [89]. The dose of 20 mg showed less effectiveness [89].

Moreover, this compound produced dose-responsive decreases in cerebral blood flow in regions of the brain known to be sensitive to drugs used to treat PD [90]. Indeed, the fMRI study revealed a decrease in thalamic cerebral blood flow in PD patients treated with tozadenant, consistent with a reduction in the inhibitory output of the BG indirect pathway [90].

On the basis of these positive findings, an international, double-blind, phase II trial of 12 weeks' duration (NCT01283594) has been performed to evaluate the effects of four doses (60, 120, 180 or 240 mg BID) of tozadenant versus placebo, as an L-DOPA adjunctive therapy, in 420 PD patients experiencing *wearing-off* and to determine dosages for the phase III clinical trial [91]. The primary goal of the study was to determine the efficacy of tozadenant in reducing the *off-time*. The trial also assessed the safety of tozadenant and its impact on various measures of motor symptom severity, dyskinesia and non-motor symptoms [91, 92]. In this phase II trial, tozadenant displayed clinically relevant and statistically high significant effects in PD patients, such as a decrease in *off-time* (120 mg BID: -1.1 h, $p = 0.0039$; 180 mg BID: -1.2 h, $p = 0.0039$), an increase in *on-time*, an improved motor UPDRS score (120 mg BID: -2.2, $p = 0.0325$; 180 mg BID: -2.5, $p = 0.0325$) and non-motor UPDRS score (all doses, $p \leq 0.03$) as well as improvements in clinician- and patient-assessed global impression scores [92]. Moreover, the amount of time patients spent in the *on-time* with troublesome dyskinesia was not significantly increased in any tozadenant group [92].

Furthermore, tozadenant in both phase II trials was generally well tolerated with no serious AEs. The most common AEs in the combined tozadenant groups were dyskinesia, nausea, dizziness, constipation, PD worsening, insomnia and falls [87, 89, 92]. Hence, the doses of 120 and 180 mg BID of tozadenant were identified as clinically useful target doses for the phase III trial [87, 92].

4.5 V81444

The new-generation compound V81444 (BIIB34) was designed to address the chemical structural liabilities that may have led to the toxicity concerns of the already discontinued compound vipadenant (described in a later section) [93].

A phase I trial (NCT01634568) to investigate the safety, tolerability and pharmacokinetics of single and multiple ascending doses of V81444 has been performed in 49 healthy male volunteers (Table 2) [94]. This phase I study has demonstrated that V81444 has a good safety and tolerability profile in healthy volunteers and has identified the dose range to be evaluated in the planned receptor-occupancy study [95].

The pharmacokinetic profile of the compound was found to be uncomplicated, with good drug concentrations in plasma that increased with increasing doses. Both single dose and repeated administration for 14 days across a wide range of doses were found to be well tolerated with no unexpected safety findings [95].

A receptor occupancy study, using PET scanning, was then performed to evaluate the relationship between dose, plasma concentration and blockade of the A_{2A} receptor [96]. This study also included a preliminary investigation, using fMRI, of the effects of V81444 on cognitive function [96]. The receptor-occupancy study demonstrated that full A_{2A} blockade could be achieved with single doses that were within the range of doses previously shown to be well tolerated with no safety concerns, and provided confirmation of the appropriate dose to be used in the next phase II clinical trial [96].

A phase II proof-of-concept study to further evaluate the pharmacokinetics, safety and tolerability of V81444 in patients, together with an evaluation of efficacy in a target patient population, has been planned by the company [97]. In particular, this randomized, double-blind, placebo-controlled, phase II trial will evaluate the safety, tolerability, pharmacokinetics and anti-parkinsonian activity of V81444 after BID administration for 14 days in 24 subjects with a confirmed diagnosis of PD. The trial is being conducted at a single US site [97].

5 Discontinued A_{2A} Antagonists

Recently, two non-xanthine A_{2A} antagonists, preladenant and vipadenant, have been discontinued by their company for different reasons. In this section, clinical findings of these compounds have been reviewed in order to give some general information on all the clinical trials performed so far using A_{2A} antagonists as anti-parkinsonian agents, and to try to clarify the problems detected during the trials of these discontinued compounds.

5.1 Preladenant

Preladenant (SCH-420814) is a non-xanthine adenosine A_{2A} antagonist. It was derived from the well known SCH58261, a pharmacological tool widely used to characterize the A_{2A} receptor subtype [98], in order to improve its pharmacological features. Indeed, preladenant exhibits high affinity for human A_{2A} receptors, with Ki values of 1.1 nM (Table 1), and high selectivity: 1,000-fold for human A_{2A} receptors compared with A_1, A_{2B} and A_3 receptors (Table 1) [98]. Preladenant is orally active and shows good pharmacokinetic properties and excellent in vivo activity against parkinsonian symptoms [31, 98].

A phase I trial in 48 healthy subjects confirmed the favourable pharmacokinetic properties, safety and tolerability of single (5–200 mg) and multiple doses (10–200 mg/daily over 10 days) of preladenant [99]. Moreover, a phase I PET study, using the radiotracer [^{11}C]SCH-442416 in 18 healthy humans, was undertaken to correlate plasma concentrations of preladenant (after 10, 50 and 200 mg) and receptor occupancy [100]. The radiotracer [^{11}C]SCH-442416 exhibited high affinity (Ki = 0.048 nM) and selectivity (>20,000-fold versus A_1, A_{2B} and A_3) for A_{2A} receptors [100]. The results of this phase I study showed that A_{2A} receptor occupancy by preladenant increased rapidly, and A_{2A} receptor-occupancy duration was augmented with increasing doses of preladenant, compatible with further development as a BID treatment [100].

5.1.1 *Clinical Trials of Preladenant as Adjunctive Therapy*

After two short phase II trials (BID, dosing over 1–3 days) in which preladenant, as adjunctive therapy, produced an improvement in motor function in PD patients [101], a more extensive international dose-finding phase II trial (NCT00406029) on preladenant as adjunctive therapy has been performed. In this study, the efficacy and safety of four different doses (1, 2, 5 or 10 mg BID over 12 weeks) of preladenant compared with placebo have been evaluated in 253 patients with moderate-to-severe PD experiencing dyskinesia and motor fluctuations (Table 2) [102, 103]. All patients were on a stable regimen of standard treatments with L-DOPA and other adjunctive medications, such as dopamine agonists and/or entacapone [102, 103]. Preladenant at doses of 5 and 10 mg BID was significantly more effective in reducing the *off-time* than placebo [−1.6 h ($p = 0.049$) and −1.7 h ($p = 0.019$), respectively, versus −0.5 h]. In addition, preladenant at both doses significantly increased the *on-time* compared with placebo [+1.4 h ($p = 0.024$) and +1.3 h ($p = 0.049$), respectively, versus +0.2 h), without producing a proportional overall increase in any dyskinesia (troublesome or non-troublesome) [103]; whereas the low doses of preladenant 1 and 2 mg BID were not significant in reducing the *off-time* compared with placebo ($p = 0.753$ and $p = 0.162$, respectively [103].

A similar phase II trial (NCT01294800) of preladenant (2, 5 or 10 mg BID over 12 weeks) in combination with

L-DOPA was performed in Japanese moderate-to-severe PD patients (Table 2) [104]. Moreover, a phase I trial (NCT00845000) investigated the effects of a single dose (10 or 100 mg) of preladenant on the dyskinesia and anti-parkinsonian actions of an L-DOPA infusion in PD patients (Table 2) [105]. The results of the last phase II and I trials have not yet been disseminated.

A further phase II trial (NCT00537017), a 36-week extension of the NCT00406029 trial, to assess long-term safety and efficacy of preladenant at a dose of 5 mg BID as adjunctive therapy, has been performed in moderate-to-severe PD patients who had participated in the main study (NCT00406029, Table 2) [106]. Results of this extension trial provide evidence that long-term preladenant treatment has sustained efficacy in improving *on-time* (1.2–1.5 h) and reducing *off-time* (1.4–1.9 h) in PD patients, similar to the findings seen in the previously randomized NCT00406029 trial [107].

On the basis of the efficacy demonstrated by preladenant in reducing the *off-time* in advanced PD patients, the company has performed two phase III trials (NCT01227265 and NCT01155466) with preladenant at doses of 2, 5 and 10 mg BID to evaluate its safety and efficacy to reduce *off-time* in 450 and 778 moderate-to-severe PD patients, respectively, as adjunctive therapy for 12 weeks [108, 109]. In addition, a phase III (NCT01215227) 40-week extension of the NCT01227265 and NCT01155466 trials has been planned (Table 2) [110].

5.1.2 Clinical Trials of Preladenant as Monotherapy

After promising results as adjunctive therapy in advanced PD patients, the company has performed a phase III trial (NCT01155479) with preladenant at doses of 2, 5 and 10 mg BID to evaluate its safety and efficacy as monotherapy in 1,000 early PD patients for 52 weeks (Table 2) [111]. Interestingly, in this study, rasagiline (1 mg/day) has been used as active comparator [111].

5.1.3 Safety and Tolerability of Preladenant

In clinical trials, preladenant was demonstrated to have a good safety profile and be well tolerated at all doses [99, 103, 107]. The incidence of AEs and discontinuation rates were similar between preladenant- and placebo-treated groups [103]. A small increase in systolic and diastolic blood pressure was initially observed in patients administered with preladenant [103], but this returned to baseline values when measured from 2 to 12 weeks after beginning the treatment [103]. Similarly, a transient mild increase in blood pressure occurred a few hours after preladenant administration [99]. However, no dose-dependent effect on blood pressure was detected upon careful inspection of the data from both studies [99, 103]. Moreover, a phase I (P04941) study in 60 healthy volunteers demonstrated that preladenant, at clinical and super-therapeutic doses (10 and 100 mg BID, respectively, for 5 days) was not associated with a delay of cardiac repolarization [112].

In all phase trials, the most frequent AEs reported were parkinsonism, dyskinesia, constipation and somnolence [103, 107]. There was no clinically significant drug effect on pulse, respiration, or other laboratory and electrocardiographic parameters [99, 103, 107].

5.1.4 Reasons for Discontinuation of Preladenant

Unfortunately, after an initial review of the data collected by the three completed phase III trials, (two as adjunctive therapy and one as monotherapy), which did not provide evidence of efficacy of preladenant compared with placebo, Merck decided to discontinue the extension phases of these studies, and no longer plans to pursue regulatory filings for preladenant [113]. The company reports that this decision is not based on any safety finding [113]. Despite this decision, Merck has planned to conduct further analyses of the data to inform the scientific community's efforts in finding new approaches to treat PD [113].

Importantly, preladenant has not yet been tested in PD patients in circumstances in which rodent and primate studies suggest that it may be useful; for example, as adjunctive therapy with a suboptimal dose of dopamine agonists or L-DOPA, instead of the optimal doses usually used in clinical trials, to determine whether it can potentiate the motor benefit afforded by these compounds, without producing or reducing dyskinesia. Further clinical investigation of preladenant would need to be pursued to understand its full potential as a treatment for PD.

5.2 Vipadenant

The non-xanthine compound vipadenant (BIIB014/V2006) is a triazolo[4,5-*d*]pyrimidine derivative (Fig. 1) [114]. Vipadenant displays high affinity for the A_{2A} receptor, with a Ki value of 1.3 nM, and selectivity for the A_{2A} receptor subtype (>50-fold vs A_1 and A_{2B} receptors and >1,000-fold vs A_3 receptor) (Table 1) [30].

Preclinical pharmacokinetic studies in rodents and non-human primates showed a good oral bioavailability, long plasma half-life and good brain penetration [30]. These findings have been confirmed by phase I pharmacokinetic trials (NCT01017666 and NCT00531193) in 28 and 32 healthy young and elderly humans, respectively, showing that pharmacokinetics of vipadenant was appropriate for further development of this compound as a single daily treatment (Table 2) [115–117]. Vipadenant did not display mutual pharmacokinetic interaction with other drugs,

including L-DOPA/carbidopa combination (Sinemet10/100®) [20, 117].

In particular, a phase I trial (NCT00531193) using PET with multiple doses (2.5–100 mg/daily) of vipadenant (administered orally for 8–12 consecutive days) was performed to evaluate the occupancy of A_{2A} receptors in the brain (caudate putamen, nucleus accumbens, thalamus and cerebellum) of healthy male volunteers [116, 118]. The PET receptor-occupancy trial in humans demonstrated that vipadenat was delivered to the brain and the A_{2A} receptor occupancy was related to both dose and plasma levels of this drug [118].

5.2.1 Clinical Trials of Vipadenant as Adjunctive Therapy

The pharmacological efficacy, tolerability and safety of vipadenant as an anti-parkinsonian drug was investigated in two clinical phase II trials. In the phase II trial (NCT00438607), single and repeated doses of vipadenant were administered orally (daily for 8 weeks) in association with habitual L-DOPA treatment in 83 patients with moderate-to-severe PD (Table 2) [119]. This trial demonstrated that vipadenant was efficacious, in a dose-dependent manner, as adjunct therapy in late-stage PD patients, decreasing the *off-time* and increasing the *on-time* [20, 120, 121].

5.2.2 Clinical Trials of Vipadenant as Monotherapy

The phase II trial (NCT00442780) evaluated the effect of ascending doses of vipadenant as monotherapy in 36 patients with early stage PD [122]. This trial demonstrated that vipadenant was efficacious, in a dose-dependent manner, as monotherapy in early-stage PD patients, reducing the UPDRS motor scores [20].

5.2.3 Safety and Tolerability of Vipadenant

The safety and tolerability of vipadenant have also been assessed in clinical trials in both healthy volunteers and PD patients [20, 120, 121]. A specific phase I trial (NCT010035515) was also performed to assess the effect of a single dose of vipadenant on blood pressure and haemodynamic variables in 24 healthy volunteers over 24 hours (Table 2) [123]. In all trials, vipadenant was well tolerated and no clinically significant abnormalities were seen in vital signs, electrocardiography, safety, laboratory or cognitive function tests [20, 120, 121]. Specifically, vipadenant-treated PD patients had a low incidence of AEs, which were mild to moderate [121].

5.2.4 Reasons for Discontinuation of Vipadenant

Although the results of phase II clinical trials were promising, development of vipadenant was discontinued by Vernalis and Biogen in June 2010 [124]. The two companies have since decided to progress preclinical studies of a next-generation compound, V81444, described in an earlier section [93].

6 Criticism of Clinical Trials of A_{2A} Antagonists in PD Therapy

Although clinical findings obtained with A_{2A} antagonists are not always statistically significant, they indicate clearly that these drugs reduced the *off-time* by about 1 hour per day in advanced-PD patients [16, 57, 60, 61, 63, 65, 68–70, 72, 92, 103, 120]. However, this benefit is similar to what has been observed in some other studies of PD medications approved as adjuncts to L-DOPA in patients with motor fluctuations [8]. For example, a large study evaluating the MAO-B inhibitor, rasagiline (1 mg/day), and the COMT inhibitor, entacapone (200 mg with every L-DOPA dose), demonstrated that both drugs reduced the *off-time* by about 0.8 hour per day compared with placebo ($p < 0.01$) [125–127].

It is also important to underline that the majority of PD patients in the A_{2A} antagonists trials were administered additional adjunctive anti-parkinsonian medications, such as MAO-B inhibitors, COMT inhibitors and dopamine agonists, so the benefits obtained by adding A_{2A} antagonists were in addition to those achieved with these other medications; even though, in order to clarify the real effects of A_{2A} antagonists, a specific differentiation among these adjunctive medications in PD patients was not deeply analysed in all trials.

On the basis of these considerations, it might be hypothesized that in the clinical trials with negative results, one with istradefylline and three with preladenant, using entacapone and rasagiline as active internal comparator, respectively, the effect of A_{2A} antagonists on reducing the *off-time*, has been minimized by the comparison with these active comparator drugs [73, 108–110]. Thus, in studies with negative results, A_{2A} antagonists did not appear to be as effective as MAO-B or COMT inhibitors [72, 73, 108–110]. However, compared with MAO-B and COMT inhibitors, A_{2A} antagonists offer the potential advantage of lack of interactions with antidepressants, narcotics, and tyramine [63].

In addition, another limitation of the study design is the lack of data concerning the consumption of dietary products, such as caffeine, which apparently was neither excluded nor monitored [56, 57, 60, 61, 63, 65, 68, 69, 72, 77, 92, 103, 120]. Indeed, at doses relevant to typical human consumption, caffeine binds to striatal A_{2A} receptors in vivo to a similar extent as specific A_{2A} antagonists [128]. Thus, the consumption of caffeine might interfere

with the action of concomitantly administered A_{2A} antagonists. Indeed, if specific adenosine A_{2A} antagonists were found to be more effective among PD patients consuming less caffeine, it would sustain the distinct possibility of a shared anti-parkinsonian effect through a common mechanism. Therefore, larger studies might monitor dietary caffeine intake and assess its relevance for both therapeutic use of A_{2A} antagonists and clinical trials. Moreover, together with higher doses of A_{2A} antagonists and inclusion of subjects with worse motor disease, evaluation of caffeine intake could also be very important in monotherapy studies in early PD patients.

Another controversial finding concerning clinical trials of A_{2A} antagonists is the mild dyskinesia reported by PD patients, which is principally a consequence of the *off-time* reduction and the *on-time* increase; however, this dyskinesia in the majority of trials has been reported as non-troublesome dyskinesia [60, 61, 63, 68, 69, 103]. Thus, clinical data, to date, do not provide evidence for an anti-dyskinetic effect of A_{2A} antagonists, but rather suggest that A_{2A} antagonists mildly increase dyskinesia in a dose-dependent fashion [57, 60, 61, 63, 68, 69, 103]. Results vary slightly from trial to trial and may depend, in part, on the percentage of subjects with dyskinesia at baseline and the severity of their dyskinesia. However, it is important to emphasise that preclinical and limited clinical data suggested that combined administration of A_{2A} antagonists and a lower dose of L-DOPA in PD patients with established dyskinesia might be able to maintain the anti-parkinsonian response and reduce dyskinesia [41, 43, 44, 56], but this remains to be proven. Moreover, also in this case, other potential factors may include concomitant medications such as amantadine and dietary intake of caffeine, although these factors have not been systematically evaluated. Thus, critical aspects of the potential benefits of A_{2A} antagonists with regard to dyskinesia are yet to be evaluated.

7 Conclusions

The data available to date support the development of the adenosine A_{2A} antagonists as a treatment for advanced PD.

Indeed, the observed temporal reduction of L-DOPA *off-time* is of particular interest, the *wearing-off* being one of the major disadvantages manifested during long-term use of this medication in advanced-PD patients.

Notably, the goal reached by istradefylline with its manufacturing approval is fundamental for this research field and provides the first step to extend the clinical investigation to a large PD patient population. Hence, it might now be easier to further investigate the other potential anti-parkinsonian effects of A_{2A} antagonists, including their effectiveness as monotherapy in early-stage PD patients, as well as adjunctive therapy with a low dose of L-DOPA in patients with advanced PD. Moreover, it might be possible to investigate, in more depth, their neuroprotective potential and efficacy against cognitive deficits in PD patients.

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